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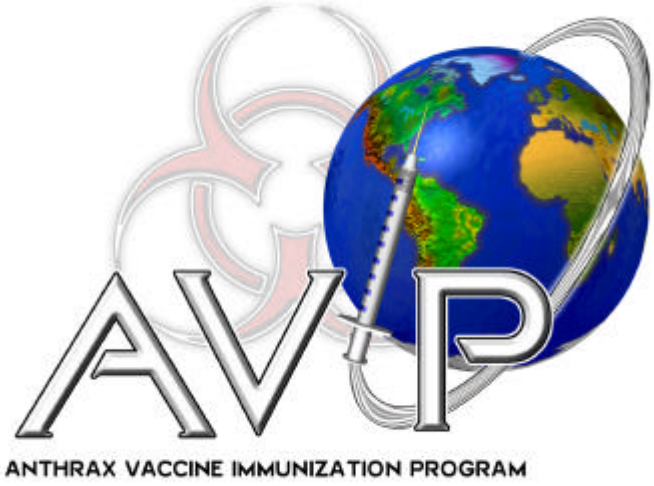

Information About the Anthrax Vaccine and the Anthrax Vaccine Immunization Program (AVIP)

Prepared by Anthrax Vaccine Immunization Program (AVIP) Group and the
Office of the Assistant Secretary of Defense (Health Affairs),
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EXECUTIVE SUMMARY

With more than a year's experience implementing the Anthrax Vaccine Immunization Program (AVIP), the results affirm that it is the right thing to do, and now is the right time to do it. The anthrax vaccine, licensed in 1970, is effective and has an excellent safety record.

Anthrax is readily weaponized, highly lethal, and poses a clear threat from potential adversaries. More than 1.1 million doses of anthrax vaccine have been given to more then 338,000 Service Members. Although local reactions at the injection area are not uncommon, such reactions are usually mild and short-lived. There have been few serious adverse events (defined by hospitalization or loss of work time greater than 24 hours). The DoD uses a civilian-based, FDA system (called VAERS) to evaluate adverse events. Reported reactions are similar to other commonly prescribed immunizations, including those required for school children and vaccines mandatory for military personnel. No unexpected patterns of adverse events have been detected to date.

The evidence of vaccine effectiveness against aerosol exposure to anthrax is persuasive. It is unethical to enter human subjects into experiments in which they are exposed to inhaled anthrax spores, but results from studies using non-human primates show that the vaccine is very effective in preventing disease, whereas all unvaccinated animals succumbed from infection.

Previous concerns about production facility deficiencies in meeting current Good Manufacturing Practices (GMP) have been addressed by FDA action and DoD assistance to the facility, with a supplemental testing program as an additional quality-control check. As with all vaccines, each lot of anthrax vaccine released has passed extensive tests for safety, sterility, purity, and potency.

Balancing the risks of immunization (low, similar to all licensed vaccines) versus the risks of disease from failing to vaccinated, the scales tip decidedly in favor of immunization. The consequences of unvaccinated unit members becoming biological warfare casualties would be tragic enough, but the consequences would be graver than their deaths alone. Their individual deaths may jeopardize the capability and survival of entire military units, as well as the success of the military mission. Just as vaccines are required for school children for the good of the community, the anthrax vaccine is mandatory for military personnel as an important force health protection measure. The Secretary of Defense, after assuring a program of high quality, directed the implementation of the Anthrax Vaccine Immunization Program for the Total Force.

Rumors alleging the presence of squalene in the anthrax vaccine are false. The anthrax vaccine never has and does not now contain squalene.

It is very important that DoD be recognized as forthright, honest, and credible. The DoD began with an assertive program to inform people about the value of anthrax vaccination. We are steadily enhancing DoD's education efforts by installing a toll-free information line (877-GET-VACC) and an authoritative Internet web site (www.anthrax.osd.mil).

It must be the policy of the United States government today and in the future to protect the Armed Forces against clear biological warfare threats when there is available a safe and effective vaccine. The anthrax vaccine is such an agent.

BACKGROUND

On December 15, 1997, Secretary of Defense Cohen approved the plan to immunize the Total Force against anthrax, contingent on four conditions: (1) supplemental testing of anthrax vaccine lots in the stockpile to assure their potency, purity, sterility, and general safety, consistent with Food and Drug Administration (FDA) standards; (2) approval of the Services' implementation plans for execution and communication; (3) implementation of a system for fully tracking anthrax vaccinations; and (4) review of the health and medical aspects of the program by an independent expert. Each of these conditions was fulfilled.

Eventually, the Total Force of approximately 2.4 million Americans, including more than 1 million members of the National Guard and Reserves, will receive the FDA-licensed anthrax immunization. The program also extends to the U.S. Coast Guard. The AVIP will be implemented in three phases over a seven- to eight-year period. Forces expected to deploy to high-threat areas will be the first immunized against anthrax. This phase, referred to as Phase I, includes Service Members and mission-essential DoD civilians assigned or deployed to Joint Staff designated high-threat areas in Southwest Asia (SWA) and Korea (i.e., Northwest Asia, NWA). Phase I began in March 1998, due to increasing tensions in the region. The Secretary himself was one of the first people vaccinated against anthrax. Phase I extended to forces deployed to Korea and surrounding waters on August 16, 1998.

Early deploying forces supporting SWA and NWA, both Active and Reserve Component personnel, will constitute Phase II. Phase III will include the remainder of the force, both Active and Reserve Component, and new personnel. As of 15 September 1999, more than 1,114,130 doses of anthrax vaccine have been given to over 337,954 Service Members in the DoD Anthrax Vaccine Immunization Program (AVIP).

HISTORY OF THE ANTHRAX VACCINE

The anthrax vaccine given to U.S. forces was licensed by the FDA on November 4, 1970. For almost 30 years, the anthrax vaccine has been recommended for at-risk veterinarians, laboratory workers, and others at occupational risk in the U.S. The manufacturer distributed about 68,000 doses of anthrax vaccine between 1974 and 1989. The FDA-licensed anthrax vaccine is effective and has an excellent safety record. It is a sterile, non-infectious product made from the filtrate of formaldehyde-inactivated bacteria. It is impossible to contract the disease from the vaccine.

Immunization with the anthrax vaccine requires six doses administered over 18 months to complete the primary series. Doses are administered at 0, 2, and 4 weeks, and 6, 12, and 18 months (where the first dose is given at "week 0"). Yearly boosters are administered thereafter to maintain immunity. Although protection levels increase as shots in the series are given, the entire six-shot series is needed.

THREAT ASSESSMENT

The biological warfare (BW) threat to U.S. forces is real. At least seven countries, including several hostile to Western democracies – Iran, Iraq, Libya, North Korea, and Syria – now possess

or are pursuing offensive BW capabilities. It is within the reach of not only rogue nations, but also transnational terrorist groups. Anthrax tops the DoD threat list. When inhaled, anthrax is highly lethal, 100,000 times more potent than the deadliest chemical warfare agent. Small amounts of anthrax can produce large numbers of casualties. A 1993 report by the U.S. Congressional Office of Technology Assessment estimated that between 130,000 and 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of the Washington, DC, area – truly a weapon of mass destruction. The accidental aerosolized release of anthrax spores from a military microbiology facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 79 cases of anthrax infection and 68 deaths and demonstrated the lethal potential of anthrax aerosols. An anthrax aerosol would be odorless, invisible, and capable of traveling many miles.

Anthrax is, by far, the easiest biological agent to produce and weaponize. Production of anthrax as a biological weapon does not require special equipment or advanced technology. It is extremely stable and can be stored almost indefinitely as a dry powder. It can be loaded in advance, as a freeze-dried powder, in munitions or disseminated as an aerosol with crude sprayers. While protective clothing and gas masks provide excellent front-line defense, their effective use requires rapid and early detection of the agent. Detection devices are not sufficient to completely protect against the threat. They may not detect an agent in time to warn personnel to don protective gear before exposure would occur.

EFFICACY OF THE ANTHRAX VACCINE

The evidence of efficacy of the FDA-licensed anthrax vaccine is based upon data from both human and animal research. The vaccine, licensed in 1970, induces immune response through a protein called protective antigen. The same protective antigen in the licensed vaccine was involved in the pivotal, placebo-controlled clinical study conducted in humans of anthrax vaccine [Brachman, et al. *American Journal of Public Health* 1962;52:632]. This study was conducted in a group of wool-mill workers in New Hampshire from 1955 to 1959.

Cutaneous anthrax (anthrax contracted through the skin) was an occupational health hazard among the mill workers for many years before the study. One group of workers was vaccinated, one group received a placebo, and another group was simply observed. The study revealed that vaccination resulted in a statistically significant reduction in the incidence of cutaneous anthrax between vaccine recipients and those not vaccinated. People who were vaccinated developed disease 93% less often than those not vaccinated. Standard statistical analyses indicate that if this study were repeated, we would expect to see disease reduction between 65% to 100%. During the course of the study, there was an outbreak of the inhalation form of anthrax. Five cases of inhalation anthrax occurred among 870 unvaccinated people, with zero cases among 379 fully vaccinated people. Despite the obvious trend, the number of cases of inhalation anthrax was insufficient for the difference between groups to reach statistical significance. Thus, efficacy of the vaccine against this form of the disease could not be demonstrated conclusively. A follow-on study by the CDC for the period 1962 to 1974 reported on 27 cases of cutaneous anthrax among unvaccinated (or only partially vaccinated) workers in or near the mills, compared to no cases among those fully vaccinated.

In non-human primates, the animal model that best approximates humans, the FDA-licensed anthrax vaccine is able to provide > 95% protection against an aerosol challenge. In one study, 20 of 21 animals immunized at 0 and 2 weeks survived. In two other studies, 9 of 9 animals and 5 of 5 animals immunized at 0 and 4 weeks survived lethal aerosol challenge. Thus, 34 of 35 animals given 2 doses of anthrax vaccine were protected against a lethal aerosol challenge. An additional study in non-human primates showed that a single dose of anthrax vaccine protected 10 of 10 animals from lethal challenge at 6 weeks. Overall, a total of 44 of 45 non-human primates vaccinated with the licensed anthrax vaccine survived a lethal aerosol challenge. In the various studies with non-human primates, a total of 14 unvaccinated animals were challenged and none survived.

In summary, although the available research on vaccine effectiveness against the highly lethal anthrax bacteria, used as a biological weapon in aerosol form, is not definitive, the animal evidence of efficacy is very persuasive. Because the incidence of all forms of naturally occurring anthrax and most particularly the inhalation form is exceedingly low, there is no opportunity to conduct well-controlled field trials and anthrax is, of course, too lethal to test on humans. Thus, there would be no opportunity to conduct human challenge studies of any vaccine or therapeutic agent against inhalation anthrax. For these reasons, the only feasible approach to evaluate the efficacy of vaccines and treatments against exceedingly rare diseases such as inhalation anthrax is to rely on the human data available, supplemented by results of animal research. The efficacy of the vaccine against geographically diverse strains of anthrax appears at Appendix A. The effectiveness of the vaccine against supposedly “vaccine-resistant” strains of anthrax is discussed in Appendix B.

SAFETY OF THE ANTHRAX VACCINE

Short-Term Safety

Several studies show that anthrax vaccine is a safe vaccine, with an incidence of side effects after injection similar to other common vaccines. Like any medicine, any vaccine will occasionally cause adverse reactions. Usually these are mild, like a sore arm or “flu”-like symptoms. Symptoms at the injection site often can be treated with over-the-counter pain relievers like ibuprofen. Pretreatment of people who developed injection-site reactions previously may minimize reactions to subsequent doses. Serious reactions are rare, but they can happen with any vaccine.

Our understanding of common side effects after vaccination come from multiple active-surveillance studies stretching from the 1950s to the 1990s. The older studies were conducted in civilian occupational settings (coordinated by CDC researchers), among U.S. Army research laboratory workers at Fort Detrick, Maryland, and elsewhere, and among U.S. military personnel in Korea, Hawaii, North Carolina, and elsewhere. In aggregate, these multiple studies are the basis for DoD confidence in the anthrax vaccine.

Based on data obtained over almost 30 years of experience with the anthrax vaccine, it is expected that up to 30% of people receiving the vaccine will experience some mild adverse effects, most commonly local reactions such as redness and soreness around the injection site.

Between 1% and 5% have a local reaction 1” to 5” in diameter. Less than 1% have larger reactions. Significant events beyond the injection site occur in less than 1% of anthrax vaccine recipients. Women develop injection-site reactions up to twice as often as men. Some vaccine recipients report symptoms that commonly occur among unvaccinated people (e.g., headaches). These rates of adverse reactions are similar to those for other vaccines, including the generally mandatory childhood vaccines, DTP (diphtheria-tetanus-pertussis), MMR (measles-mumps-rubella), and other vaccines administered to military personnel, such as hepatitis A, yellow fever, and other vaccines.

For purposes of comparison, the studies of the current anthrax vaccine submitted in the licensing application to the FDA showed that in 16,000 doses approximately 3% to 20% exhibited mild reactions and fewer than 1% severe side effects. In the case of hepatitis A vaccine, soreness at the injection site was reported by 56% of adult vaccine recipients. Headache was reported by 14%. For the typhoid vaccine, local tenderness was reported by 98%, pain by 56%, malaise by 24% and headache by 11%. The pneumococcal vaccine, which is a recommended vaccine for all Americans over the age of 65, has a 71% rate for localized soreness. The recently licensed Lyme disease vaccine produced localized pain in 93% of recipients and fever in 2.5%. The hepatitis B vaccine reports a local reaction rate of 17% and a systemic reaction rate of 15% in adults.

To monitor unusual adverse events attributed to anthrax vaccine, DoD guidance directs health-care providers to use the Vaccine Adverse Event Reporting System (VAERS). The Department of Health and Human Services established VAERS in November 1990 as a national surveillance system for vaccines, as the successor to earlier adverse-event monitoring systems. DoD has participated in VAERS since the inception of VAERS in 1990. Indeed, DoD has contributed data to various medication safety monitoring systems for many decades.

VAERS is considered a passive system, because it relies on health-care providers to report adverse events they see in clinical practice. The strength of VAERS is in recognizing unexpected and rare adverse events. It is co-managed by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC).

VAERS uses established surveillance methods. Passive systems like VAERS are known to underreport the true number of adverse events, although they underestimate common events more than rare events. For anthrax vaccine and all other vaccines, DoD *requires* its providers to report through the VAERS system all cases of (1) loss of duty for more than 24 hours; (2) hospitalization for any reaction; and (3) suspected contamination of a vaccine container. In addition, DoD *encourages* its health-care professionals to report all adverse events they consider important and clinically relevant, even if the event does not meet the aforementioned criteria. It is also important to mention that patients may report adverse events directly to VAERS if they wish.

DoD relays all reports of adverse events after any vaccination to the Food & Drug Administration. This is part of DOD's long-standing participation in FDA's Vaccine Adverse Event Reporting System (VAERS). At the request of DoD, the Department of Health and Human Services (HHS) established an Anthrax Vaccine Expert Committee (AVEC) in October 1998 to review VAERS forms related to anthrax vaccine. A distinguished university professor chairs this

review committee of civilian physicians with expertise in immunology, internal medicine, neurology, rheumatology, and microbiology. The AVEC independently reviews all anthrax vaccine-related reports received by VAERS. The Committee meets every 4 to 6 weeks, along with representatives of DoD, CDC, FDA, and HHS, to review all the new anthrax adverse events reports submitted in the interim. The AVEC reviews the quality of the submitted information, evaluates the reported event in the context of expected and unexpected adverse events to vaccines, and assesses the causal relationship of the event with the anthrax vaccine. The Committee also looks for any clinically significant patterns in the aggregate data. A committee report is generated and is sent to the Office of the Army Surgeon General through the National Vaccine Program Office in HHS. To date, the AVEC has found nothing unexpected in the side-effect profile of anthrax vaccine.

As of September 8, 1999, the independent Anthrax Vaccine Expert Committee (AVEC) had reviewed 314 VAERS reports related to anthrax vaccination. Seventeen of the 314 reports involved hospitalization; the civilian panel found that 5 of the 17 certainly or probably were caused by anthrax vaccine. All five involved allergic, inflammation reactions at the injection site. Another 72 reports involved loss of duty greater than 24 hours (but did not involve hospitalization); the civilian panel found that 50 of the 72 certainly or probably were caused by anthrax vaccine. These 50 reports described injection-site reactions (26 reports), urticaria or other rashes (14), “flu”-like symptoms (13), tingling (2), itching (1), shortness of breath (1), and bronchiolitis (1). Some reports described multiple symptoms. The balance of the 314 reports, 225, were categorized as other than serious (on a functional basis), involving neither hospitalization nor loss of duty greater than 24 hours.

Separate analyses performed by the Anthrax Vaccine Immunization Program indicate that there has been no correlation between anthrax vaccine and reports of serious adverse events (involving hospitalization or loss of duty) based on (a) geographic clustering, (b) vaccine lot (manufacturing batch), or (c) active vs. reserve component status. No VAERS reports have been submitted regarding microbial contamination of vaccine vials. There have been no deaths related to anthrax vaccination.

The FDA-licensed anthrax vaccine was also used during the Persian Gulf War to immunize approximately 150,000 American personnel against Iraq’s biological weapons. Several national civilian scientific groups, including the Presidential Advisory Committee on Gulf War Veterans’ Illnesses, the Institute of Medicine, the National Institutes of Health, and the Defense Science Board, have closely examined this issue and found no evidence to link the FDA-licensed anthrax vaccine with illnesses among Gulf War veterans. These reports can be viewed in their entirety on the Internet at addresses listed in Appendix C.

Severe reactions reported close in time after vaccination have been few. With over 1.1 million anthrax vaccinations given to Service Members under the Anthrax Vaccine Immunization Program, the low incidence of reported serious adverse events confirms expectations regarding the short-term safety of the vaccine.

In reviewing safety and adverse reactions regarding any vaccine, it is important to be mindful of the context. As stated by the CDC (in CDC Publication, "Surveillance for Adverse Events

Following Vaccination," September 1997; http://www.cdc.gov/nip/vacsafe/vaccinesafety/publications/aesurveillance.htm):

> Immunizations have reduced the incidence of many vaccine-preventable diseases in the United States (and many other countries) by more than 95% compared with the pre-vaccine era. . . . As the proportion of the population vaccinated increases, however, the number of persons who experience an adverse event following vaccination also increases due either to true reactions caused by the vaccination or coincidental events not caused by the vaccination. In recent years, the annual number of reports to the Vaccine Adverse Event Reporting System (VAERS) have exceeded the total number of reports of routine childhood vaccine-preventable diseases … [due to the effectiveness of vaccines in preventing infectious disease].
>
> Vaccines are usually administered to healthy persons and often are mandatory; therefore, they are held to a higher standard of safety than other medications. However, as with all medications, no vaccine is perfectly safe or effective. Vaccines can induce minor adverse events such a local reaction or fever. Very rarely, they can induce serious adverse events . . . . To assure that vaccines are as safe as possible and to maintain public confidence in vaccines, close monitoring of the incidence of adverse events, adequate scientific evaluation of possible associations, and appropriate responses to newly identifies risks of vaccines are essential.

A summary of short-term studies that reviewed side effects is attached at Appendix D.

Long-Term Safety

The DOD leadership, its physicians, and its research experts are confident of the safety and efficacy of the anthrax vaccine. The confidence is based on experience with anthrax vaccination of about 1,700 laboratory workers at Fort Detrick, Maryland, and other studies. Most of these workers received 150 to 200 vaccinations and skin tests; some received more than 300 such injections during their tenure at Fort Detrick. Many received annual booster doses of anthrax and other vaccines for 10 to 20 or more years. The first report of this group of vaccine recipients was published in the *Bulletin of the Johns Hopkins Hospital* in 1958. Two follow-up reports were printed in the *Annals of Internal Medicine* in 1965 and 1974. An update is currently being prepared.

An extension of this long-term study is underway to determine, in even greater detail, whether individuals who received multiple vaccines, including anthrax vaccine, during their past employment at Fort Detrick demonstrated any adverse health effects over the long term. A total of 570 study and control volunteers have been enrolled in this case-control study begun in 1996. All volunteers signed an informed-consent document. The study methods include a 9-page health history questionnaire, extensive blood tests and urinalysis. The questionnaire queries mental and physical conditions of progeny as well as the health of volunteers. Study end points include symptoms, symptom complexes (including the complex of symptoms reported by veterans of the Persian Gulf War), diseases, and abnormal laboratory and urine tests. Study subjects will be compared to two to three race-, gender-, and age-matched control subjects to determine if any

long-term medical effects exist among this unique group of study subjects. Analysis of the data from the extensive health history questionnaire and numerous laboratory tests is currently in progress.

Our leaders respect the concerns expressed by Service Members about the possibility of long-term health effects and want to address these concerns using the most appropriate scientific knowledge and practices. We will continue our ongoing commitment to ensuring the health of our men and women as we implement the AVIP.

On August 24, 1999, the Anthrax Vaccine Immunization Program convened a team of civilian and military medical experts to set a research agenda to gather additional information about the long-term safety of anthrax vaccine. In designing these studies, we will draw from the accumulated experience of some of the nation's best vaccine researchers at CDC and FDA. At the initial committee meeting, the attendees suggested two major groups of studies: retrospective (look-back) studies to collect additional information more quickly and prospective (look-forward) studies that are more scientifically rigorous.

One of the methods likely to be used is a surveillance technique used by CDC in post-marketing studies: large, linked databases. DoD will utilize the large, linked database approach in its long-term research efforts through access to its immunization tracking programs database and though the medical databases maintained by the Defense Medical Surveillance System (DMSS).

EFFECTS ON REPRODUCTIVE HEALTH

According to the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP), "there is no convincing evidence of risk from vaccinating pregnant women with inactivated virus or bacterial vaccines or toxoids." Similarly, no evidence exists that indicates any other adverse reproductive effects including effects on fertility. Indeed, some inactivated vaccines are specifically advocated by the ACIP, the American College of Obstetricians & Gynecologists, the American Academy of Pediatrics, and the American College of Physicians for susceptible women during their pregnancy. These vaccines protect against tetanus, influenza, and meningococcal disease.

Inactivated vaccines licensed by the FDA include the anthrax vaccine and a host of other vaccines that protect children and adults against diseases such as tetanus, hepatitis A, and diphtheria. The FDA does not require, as a condition of licensure, reproductive toxicity studies to determine the effect of these sterile, inactivated vaccines on pregnancy, fertility, or other reproductive functions. As a result, the package insert for the anthrax vaccine, and these other FDA-licensed vaccines, note that animal reproductive studies have not been conducted for the vaccine and that the vaccine has not been evaluated for its potential to impair fertility. This results from the virtual absence of reproductive problems caused by vaccines throughout the 20th century.

Even though the FDA-licensed anthrax vaccine is a bacterial vaccine that contains only non-living components of the anthrax organisms and is non-infectious, prudent medical practice is to defer immunizations during pregnancy unless clearly needed. Pregnant women should not

receive the anthrax vaccine unless anthrax exposure occurs or is imminent. Service Members who believe that they may be pregnant are instructed to inform their health-care provider. Anthrax immunizations will be deferred until the pregnancy is complete. Since the vaccine contains no infectious substance, there is no reason for a woman to delay becoming pregnant, nor to stop breast-feeding after receiving a dose of the anthrax vaccine. These guidelines are consistent with those of the ACIP, the American College of Obstetricians & Gynecologists, the American Academy of Pediatrics, and the American College of Physicians.

ANTHRAX VACCINE PRODUCTION ISSUES

The anthrax vaccine production facility, currently owned and operated by BioPort Corporation, has been manufacturing vaccines for decades in Lansing, Michigan. Prior to 1998, the facilities were owned by the State of Michigan and known as the Michigan Biologic Products Institute. In recent years, the manufacturer has upgraded and added to its existing facility in a staged fashion to comply with current good manufacturing practices (cGMPs). The manufacturer closed the anthrax production line in January 1998 for planned renovation. Although the decision to close the facility for planned renovation was part of the manufacturer's facility improvement strategy, it was, in part, also based on a 1996 DoD assessment that concluded that the facility was inadequate to meet future production requirements. This renovation project cost $3.7 million and included upgrades of the anthrax vaccine manufacturing space along with the addition of a negative air pressure sink, a reach-in environmental chamber, and a state-of-the-art closed inoculation system. The physical aspects of the renovation were completed in January 1999. Validation and FDA inspection of the facility must occur before full production resumes. These events are scheduled for completion in early 2000. As BioPort is the only manufacturer of FDA-licensed anthrax vaccine, DoD provided $11.3 million since 1991 to ensure a continuous supply of anthrax vaccine. In addition to monetary support, the DoD has provided significant administrative, scientific, technical, and consultative assistance to BioPort.

DoD knows that the manufacturer underwent FDA inspections in November 1996 and February 1998 that found deficiencies related to compliance with cGMPs. The FDA also acknowledged that the manufacturer had made progress toward implementing its strategic plan for achieving compliance with FDA standards and regulations. The manufacturer released a Strategic Plan for Compliance on 9 April 1997 that details how to implement quality systems and cGMP improvements to achieve compliance with applicable FDA standards and regulations. FDA found no deficiencies serious enough to warrant recall of the anthrax vaccine, which is within FDA's authority.

As an additional quality check, Secretary Cohen ordered DoD to establish a process for supplemental testing of stockpiled vaccine by the manufacturer to assure its sterility, safety, potency and purity. The supplemental testing program reaffirms FDA standards, to assure Service Members and the public that the vaccine stockpile is safe and potent. Supplemental testing repeats tests required by the FDA for lot release. An independent contractor (Mitretek Systems, Inc., McLean, Virginia) oversees supplemental testing by the manufacturer. Supplemental tests performed by the manufacture include:

- General Safety: Follows Title 21 Code of Federal Regulations (CFR) section 610.11 guidelines. General safety is determined in the following manner: two animals each of two species (mouse and guinea pig) are given doses of the vaccine and observed for 7 days for adverse effects; and the passing result is that each animal survives the test period, gains weight, and does not show any adverse reaction. Twenty vials per lot are tested for general safety.
- Potency: Follows 21 CFR 610.10 guidelines. Potency is determined in the following manner: three serial dilutions of vaccine are used plus one control group (no vaccine) to vaccinate guinea pigs; 14 days after vaccination, all guinea pigs are injected with known amounts of virulent anthrax; average time to death is calculated for each group; and the passing result is that the test vaccine is no less potent than the reference vaccine. Two vials per lot are tested for potency.
- Sterility: Follows 21CFR 610.12 guidelines. Sterility testing is performed on the final product to detect the presence of microorganisms. Twenty vials per lot are tested for sterility, using two separate culture media: fluid thioglycollate medium and soybean-casein digest medium.
- Purity: No formal 21 CFR requirements for individual testing of preservatives or additives. Only general requirements for calibration and controls. Purity testing consists of four individual tests for aluminum, benzethonium chloride, and formaldehyde. Five vials per each substance per lot are tested for purity.

As of September 1999, 10 of 31 lots have passed all supplemental testing requirements. DoD has approved these lots for use. Another 21 lots are pending resolution of testing issues that require further analysis. Each lot of vaccine consists of approximately 200,000 doses or 20,000 vials of anthrax vaccine. Each vial contains ten doses.

While the FDA inspection results were significant, the manufacturer's improvements to quality systems, cGMPs, and facilities, in conjunction with DoD support, provide assurance that the current and future anthrax vaccine inventory complies with FDA requirements. BioPort remains vital to U.S. national interests. Maintenance of this critical industrial base is essential to protect Service Members from the significant threat of anthrax as a biological weapon.

Several recent articles in magazines and newspapers have incorrectly reported that certain lots or vials of anthrax vaccine were contaminated. At no time have contaminated lots or vials of anthrax vaccine been administered to our Service Members or shipped by DoD to any military facilities. Details appear in Appendix E.

Analyses performed by the Anthrax Vaccine Immunization Program Group indicate that there has been no correlation between anthrax vaccination and reports of serious adverse events (those involving loss of duty > 24 hours or hospitalization) based on (a) geographic clustering, (b) vaccine lot (manufacturing batch), or (c) active vs. reserve component status. No reports have been submitted of potentially contaminated vaccine vials.

SQUALENE

A persistent rumor circulates that the anthrax vaccine contains a substance called squalene, claimed to cause illnesses among Gulf War veterans. Squalene is a naturally occurring substance found in plants, animals, and humans. It is manufactured in every human body as part of the process of making cholesterol and hormones. Squalene is also found in a variety of foods, cosmetics, health supplements, and over-the-counter medications.

Squalene has been used as an adjuvant (a substance used to improve the body's response to a vaccine) in some investigational vaccines manufactured in the U.S., including vaccines being tested for HIV disease, and in an influenza vaccine licensed in Europe. Whatever the arguments for or against squalene as a vaccine adjuvant, the fact is that none of the FDA licensed vaccines that were administered to U.S. troops during the Gulf War contained squalene as a vaccine adjuvant. This includes the anthrax vaccine, which does not contain squalene and never has contained squalene. The FDA has licensed only aluminum salts (e.g., aluminum hydroxide, aluminum phosphate, aluminum potassium sulphate) as adjuvants.

The Department of Defense (DoD) has never exposed any military member or civilian to any squalene-containing investigational product without the person's informed consent, abiding by FDA regulations. The DoD has conducted five human clinical trials using investigational vaccines containing squalene—investigational vaccines for the prevention of malaria and HIV infection—in FDA-approved vaccine studies. Two of the malaria vaccine studies involving a total of 17 human volunteers were conducted before or during the Persian Gulf War. Although it is unlikely, some of these subjects may have been involved in the Gulf War. Nevertheless, these investigational vaccines were part of FDA-approved studies that followed FDA guidelines for the use of investigational vaccines, to include the informed consent of the subject.

In their effort to explain the health problems of some Gulf War veterans, however, a few investigators have theorized, and the press has amplified their speculation, that a vaccine adjuvant may have caused an autoimmune disease in veterans. A recent *Vanity Fair* article "The Pentagon's Toxic Secret" (May 1999) alleges that the DoD possibly used "an illicit and secret anthrax vaccine" on its own soldiers. The writer's interpretation and presentation of the facts regarding the Department's use of anthrax vaccine are speculative, inflammatory, and wrong. His allegations and the reported "clinical evidence" are not new. Since 1997, reports in the *Washington Times* and its magazine *Insight on the News* have made similar allegations regarding an experimental "anti-HIV vaccine."

The investigators cited in the *Vanity Fair* and *Insight on the News* articles (Pamela Asa, Ph.D., Memphis, TN and Robert Garry, Ph.D., Tulane University School of Medicine, New Orleans, LA) report that they have developed and patented a test for anti-squalene antibodies. Autoimmune Technologies, LLC, of New Orleans, has an exclusive license on the use of the test. With their test the investigators report that they have detected anti-squalene antibodies in the blood of ill Gulf War veterans. To date, they have not published their findings in the peer-reviewed medical literature, nor have other researchers had access to their test methods.

The U.S. General Accounting Office (GAO) has released a report "Gulf War Illnesses: Questions about the Presence of Squalene Antibodies in Veterans Can be Resolved" (GAO/NSIAD-99-5). The Department of Defense disagreed with the GAO's opinion that "the first step is to determine

the extent to which they [antibodies to squalene] are present in a larger group of sick Gulf War-era veterans." The medical significance and the origin of antibodies to squalene, even if their existence is corroborated, remain unknown. Without such information, Gulf War veterans get only speculation about the meaning of the test result and its implication for their health. Gulf War veterans deserve objective evidence and recommendations based on sound science.

The Department of Defense also disagreed with the GAO's recommendation that the Department "conduct its own research designed to replicate or dispute these results." The accepted forum for validating or disputing the integrity of medical research findings or clinical hypotheses is to subject the work to peer review by scientists through presentation at scientific meetings and publication in peer-reviewed scientific publications. The purported assay for anti-squalene antibodies has not been validated at other laboratories.

To dispel unfounded rumors regarding the presence of squalene in the anthrax vaccine, the DOD recently contracted with an independent civilian laboratory, Stanford Research Institute (SRI) International of Menlo Park, California, to test for the presence of squalene in every lot of the anthrax vaccine released to DOD. SRI International tested 13 lots of anthrax vaccine and reported that no squalene was detected in any of the 13 lots. The DOD will test all other lots of anthrax vaccine in the stockpile when the allegations arose. Graphic images of the test results are posted at www.anthrax.osd.mil.

THE NEED FOR TOTAL FORCE ANTHRAX IMMUNIZATIONS

The DoD must provide U.S. forces with reasonable levels of protection against battle and non-battle threats to health and well being. Medical protective countermeasures, such as vaccines, are safe and effective ways to protect the health and lives of U.S. Service Members against biological warfare (BW) attack. The anthrax vaccine can be administered well in advance of deployment to high-threat areas. Unlike physical protective devices (e.g., gas masks), the anthrax vaccine protects without requiring warning or detection of a BW attack.

The anthrax vaccine has an excellent safety record and is effective. No vaccine, indeed no medication, can offer assurances that it is both 100% effective and 100% free of adverse effects. As in countless other health-care decisions, whether with a single patient or a whole population, the decision comes down to a comparison of the risks of medical intervention versus the risks of disease from not vaccinating. The risks of receiving the FDA-licensed anthrax vaccine are consistent with other commonly used vaccines, including temporary local reactions at the injection site or common systemic symptoms like headache or muscle ache. Most of these events last less than 72 hours. A smaller number will have somewhat larger injection-site reactions. A very small number will have serious reactions, characterized by hospitalization or lost work time of more than 24 hours. There are no known or suspected long-term (delayed) adverse effects of the vaccine, just as there are none with other inactivated vaccines. The risk from not immunizing Service Members against anthrax is not acceptable. The deaths of large numbers of U.S. soldiers, sailors, airmen, or marines is likely if unvaccinated troops are exposed to this potent and lethal threat. Today's military force, including both active and reserve components, is highly mobile and deployable to high-threat areas on short notice. The risk-versus-risk balance clearly requires Total Force immunization.

A broad national consensus has formed to increase the readiness of the United States to protect itself against chemical and biological warfare and terrorism threats to both military forces and civilian populations. A major part of this program is the development of new drugs and vaccines for medical protection or antidotes. The Department of Defense has established the Joint Vaccine Acquisition Program to develop and produce new vaccines for a number of high-threat biological warfare agents. The Department of Health and Human Services has established a related initiative responding to the threat to civilian populations. This is an enormous civilian and military preparedness challenge for the United States, one that will require a major commitment of resources, energy, expertise, and thoughtfulness. At multiple decision points, questions arise about the strength, depth, breadth, and meaning of the research results, the data collection methods, the project designs, the need for more studies, the urgency of decision, and other complex considerations. We all face a daunting challenge to work together to develop new products that are safe, effective, well tolerated, and suitable for stockpiling or surge production.

In the case of anthrax vaccine, the current FDA-licensed vaccine is not ideal. The vaccine was developed in the 1950's and 1960's by the state-of-the-art procedures at that time, and licensed in 1970. Advances in biotechnology and genetic engineering may enable improvements in the vaccine that allow fewer doses or use of highly purified protective antigen. The DOD scientists are pursuing both of these objectives. A highly-purified recombinant protective antigen vaccine has shown efficacy in animal models. Negotiations are underway with the National Institute of Allergy and Infectious Diseases to jointly develop this next-generation anthrax vaccine for both the Armed Forces and the civilian community. However, licensure of a new anthrax vaccine will take many years. We are unwilling to leave Service Members vulnerable to the threat while waiting for the next-generation vaccine to work its way through the research-and-development pipeline and FDA review.

If the United States is to progress in developing a credible medical defense against biological weapons attack, it will need an aggressive research-and-development program and broad consensus from scientific and medical community. Today, there is a broad consensus that the FDA-licensed anthrax vaccine is safe and effective for people at high risk of exposure. Recent publications of the CDC [ftp://ftp.cdc.gov/pub/ Publications/mmwr/wk/mm4804.pdf] and the Johns Hopkins Center for Civilian Biodefense Studies [http://www.ama-assn.org/sci-pubs/journals/archive/jama/vol_281/no_18/jst80027.htm] recognize the anthrax vaccine as part of the national preparedness against biological terrorism. In balancing of risks of immunization versus risks from failing to vaccinate, the scales tip decidedly in favor of immunization. It must be the policy of the United States government today and in the future to protect the armed forces against clear biological warfare threats when there is available a safe and effective vaccine.

MANDATORY ANTHRAX IMMUNIZATION

DoD policy requires that Service Members, emergency-essential DoD civilian and contractor personnel assigned or rotating to high-threat areas, and those pre-designated for immediate contingency deployment to these areas, will be administered the anthrax immunization first. To set an example for all Service Members, the senior leadership in the DoD, including Secretary of

Defense Cohen, Deputy Secretary of Defense Hamre, and the Chairman of the Joint Chiefs of Staff, General Shelton, were among the first people to receive the anthrax vaccination.

Choosing to be vaccinated is not an isolated decision that can be left to the personal choice of individuals. In the military, the risk from being vulnerable to infection affects the capability of the entire military unit and the success of the military mission. Military regulations require many vaccines for military personnel. Some vaccines are given to all military personnel, whereas others are given just to certain occupational groups or based on geographic assignments. For the affected category of personnel at risk, none of these vaccines is optional or voluntary; all are mandatory and provide a basis for a lawful order to a Service Member to be vaccinated. An analogy is that the risk-versus-risk balance for childhood diseases results in required vaccinations for school children. The risk of not immunizing presents a threat to the health of the community that extends beyond personal health concerns. In 1905, the United States Supreme Court affirmed the right of states to pass and enforce compulsory immunization statutes (Jacobson v. Massachusetts). In 1922, the Supreme Court similarly affirmed laws requiring vaccination before school entry (Zucht v. King).

Service Members who disobey a lawful order to take the anthrax immunization are subject to administrative or disciplinary actions. There is no DoD-wide policy directing a specific disposition when a Service Member refuses a lawful military order. The Military Services have also not enacted policies dictating a specific Service-wide response. Rather, in these instances, the local military commanders apply the principles in the Uniform Code of Military Justice (UCMJ) and the guidance in the Manual for Courts-Martial and Service regulations that apply to other cases involving a refusal to obey a lawful order.

The UCMJ, enacted by Congress over 50 years ago, and the Manual for Courts-Martial provide guidance on how commanders are to resolve misconduct. The commander's disposition decision is based on the facts and circumstances of each individual case. This requires a careful evaluation and balancing of several factors, such as the nature of the offense; the existence of other charges; mitigating or extenuating circumstances; and the character and military service record of the member. Even cases involving similar misconduct may be resolved differently based on a commander's assessment of what will best further the needs of the military and the Service Member. The Manual for Courts-Martial requires commanders to deal with allegations of misconduct in a timely manner at the lowest appropriate level of disposition.

Although authorized to use appropriate means to ensure that military personnel are properly protected, no Service Members have been restrained or physically forced to take the anthrax immunization.

EDUCATION AND COMMUNICATION

The DoD has long recognized the importance of a robust and responsive education and communication plan regarding anthrax vaccine. The Department has recently undertaken several additional initiatives, including:

- Operating a toll-free information line (1-877-GET-VACC) to respond to questions about the anthrax vaccine and the AVIP (in operation since 28 July 1999).
- Organizing a Speakers Bureau to conduct AVIP open-house forums, staff assistance visits, briefings, press conferences, and training on immunization tracking systems.
- Expanding a detailed DoD AVIP website at www.anthrax.osd.mil. The website will give DoD the capability to perform online email queries/responses (avip@otsg.amedd.army.mil).

CONCLUSION

Anthrax is a deadly biological weapon that represents a real and present danger to U.S. service personnel. The FDA has licensed the anthrax vaccine for nearly 30 years as safe and effective in preventing this extremely lethal disease. The Secretary of Defense, after assuring a program of high quality, directed the Anthrax Vaccine Immunization Program for the Total Force. The number of vaccinations given to date exceeds 1.1 million doses, with very few serious adverse events. Reports of adverse events are consistent with expectations based on previous research studies and in line with experiences with commonly used vaccines, including other vaccines required for school children and military personnel. The evidence of vaccine protection in humans and animals against aerosol exposure to anthrax is persuasive. Concerns about previous deficiencies by the production facility in meeting current Good Manufacturing Practices have been addressed by FDA action, DoD assistance to the facility, and a supplemental testing program on the safety, sterility, purity, and potency of the vaccine. Hypotheses and Internet rumors about squalene in the anthrax vaccine are false. In balancing the risks of immunization versus risks from failing to vaccinate, the scales tip decidedly in favor of immunization. The United States government must protect the Armed Forces against clear biological-warfare threats, whenever safe and effective vaccines are available.

APPENDIX A
EFFICACY STUDIES

The evidence of efficacy of the FDA-licensed anthrax vaccine is based upon data from both humans and animal models. The vaccine, licensed in 1970, is composed of a sterile filtrate from the culture of a weakened (attenuated) strain of *Bacillus anthracis* that is then attached (adsorbed) to the adjuvant aluminum hydroxide. The principal protective component of the licensed vaccine is a protein called protective antigen. The pivotal placebo-controlled clinical study conducted in humans [Brachman et al. *American Journal of Public Health* 1962;52:632] to evaluate efficacy used a vaccine similar but not identical to the current licensed anthrax vaccine. After the Brachman study, the manufacturing method was altered slightly to increase the quantity of protective antigen and increase purity by reducing levels of edema factor and lethal factor. However, both the vaccine used in the Brachman study and the current licensed vaccine were based on the immunity induced by the protective antigen.

Cutaneous anthrax (anthrax contracted through the skin) was an occupational health hazard among wool mill workers for many years. In the Brachman study, one group of workers was vaccinated, one group received a placebo, and another group was simply observed. The study revealed that vaccination resulted in a statistically significant reduction in the incidence of cutaneous anthrax (93% less disease, with a 95% confidence interval of 65% to 100% effectiveness) between vaccine recipients and those not vaccinated. During the course of the study, there was an outbreak of the inhalation form of anthrax. Five cases of inhalation anthrax occurred among 340 unvaccinated people, with zero cases among 793 fully vaccinated people. Despite the obvious trend, the number of cases of inhalation anthrax was insufficient for the difference between groups to reach statistical significance. Thus, efficacy of the vaccine against this form of the disease could not be demonstrated conclusively. A follow-on study by the CDC for the period 1962 to 1974 reported on 27 cases of cutaneous anthrax among unvaccinated (or only partially vaccinated) workers in or near the mills, compared to no cases among those fully vaccinated.

Bacillus anthracis, the causative agent of anthrax, is considered to be one of the most likely biological weapons for terrorism or warfare. The most common form of naturally occurring disease is cutaneous, acquired through the skin after handling infected animal tissue or contaminated animal products. However, the form of the disease acquired as a result of a biological attack would most likely be inhalation anthrax caused by inhaling an aerosol of anthrax spores into the respiratory tract. The incidence of all forms of naturally occurring anthrax and most particularly the inhalation form is exceedingly low. In the U.S. over the past 10 years, there has been less than one case per year reported, and all have been the cutaneous form. Thus, there would be no opportunity to conduct well-controlled field trials of any vaccines or antibiotic treatment against inhalation anthrax. Furthermore, the high mortality associated with this form of the disease would preclude any human challenge studies as have been conducted with other infections that are much milder and more easily treated once symptoms develop.

For these reasons, the only feasible approach to evaluate the efficacy of vaccines and treatments against exceedingly rare diseases such as inhalation anthrax is to rely on the use of experimental animal models. Several experimental animal models, including guinea pigs, rabbits, and non-

human primates, have been used to evaluate the efficacy of anthrax vaccines. Each species will be discussed here separately. The most persuasive data is from nonhuman primates.

In the non-human primate, the animal model that best approximates humans, the FDA-licensed anthrax vaccine is able to provide close to 100% protection against an aerosol challenge. In one study, 20/21 animals immunized at 0 and 2 weeks survived [Ivins et al. *Salisbury Medical Bulletin* 1996;87:125]. In a second study 9 of 9 animals immunized at 0 and 4 weeks survived [Pitt et al. *Salisbury Medical Bulletin* 1996;87:130]. In a third study, 5 of 5 animals immunized at 0 and 4 weeks survived lethal aerosol challenge. Thus, 34 of 35 animals given 2 doses of anthrax vaccine were protected against a lethal aerosol challenge using a strain that killed approximately 80% of vaccinated guinea pigs challenged by the aerosol route. A fourth study in non-human primates showed that a single dose of anthrax vaccine protected 10 of 10 animals from lethal challenge at 6 weeks [Ivins et al. *Vaccine* 1998;16:1141]. Overall, a total of 44 of 45 (98%) non-human primates vaccinated with the licensed anthrax vaccine survived a lethal aerosol challenge. In the various studies with non-human primates, a total of 14 controls (unvaccinated animals) were challenged and none survived.

The rabbit has also been used to evaluate the anthrax vaccine. In a study not yet published, 9 of 10 rabbits immunized with 2 doses of FDA-licensed anthrax vaccine survived lethal aerosol challenge. In a subsequent study, a total of 48 rabbits immunized with 2 doses of vaccine (28 were given a full dose of vaccine and 20 were given a quarter-dose) all survived aerosol challenge [Pitt et al. Presented at 3rd International Conference on Anthrax, 1998, abstract in press]. Thus, in various experiments, 57 of 58 rabbits (98%) immunized with anthrax vaccine survived lethal aerosol challenge. In these studies, none of a total of 28 unvaccinated control animals survived the challenge. The rabbit, therefore, is like the non-human primate in that immunization with anthrax vaccine confers excellent protection against aerosol challenge.

Primate and rabbit data contrasts with the guinea pig model where immunization with anthrax vaccine gives less consistent results. Anthrax vaccination of guinea pigs provides relatively less protection overall, less protection against aerosol exposure, and less protection against some strains of anthrax. In recent years, most experimental animal studies have used the Ames strain of *B. anthracis* for challenge. In the guinea pig model, the FDA-licensed anthrax vaccine can confer varying protection against an intramuscular challenge with the Ames strain, with 13% to 90% of animals surviving in various experiments [Turnbull et al. *Infect. & Immun.* 1986;52:356; Ivins et al. *Vaccine* 1994;12:872; Fellows, et al. Presented at 3rd International Conference on Anthrax, 1998]. However, the anthrax vaccine has been unable to provide good protection in the guinea pig against an aerosol challenge, where only 20% to 26% of the animals survived [Ivins et al. Vaccine 13:1779 (1995)].

APPENDIX B
EFFECTIVENESS AGAINST "VACCINE-RESISTANT" STRAINS OF ANTHRAX

There have also been animal studies assessing the efficacy of the anthrax vaccine against geographically diverse strains of *Bacillus anthracis*. Older studies in guinea pigs suggested there were some strains, including Ames, that were more difficult to protect against than others after anthrax vaccination [Auerbach & Wright. *J. Immunol*. 75:129 (1955); Little & Knudson. *Infect. & Immun*. 52:509 (1986); Turnbull et al. *Infect. & Immun*. 52:356 (1986)]. This led to the use of the term "vaccine-resistant" strains. But this is a relative term. In the most definitive study reported, using defined challenge doses and larger numbers of animals per group to provide better statistical power, the overall survival rate after varying doses of an intramuscular challenge of immunized guinea pigs with a "vaccine-sensitive" strain was 89%, compared to 63% for the "vaccine-resistant" Ames strain (Ivins et al. *Vaccine* 1994;12:872. Obviously, vaccines were substantially protective in both tests.

In the non-human primate aerosol-challenge model, vaccination has been shown to protect against two strains, including the so-called "vaccine-resistant" Ames strain. Ongoing experiments are testing the effectiveness of the anthrax vaccine against a geographically diverse collection of anthrax strains. In the guinea pig intramuscular-challenge model, vaccination protected against 8 of 32 such strains to the same degree as did the Ames strain [Fellows et al. Presented at 3rd International Conference on Anthrax, 1998]. Six of these strains were then used to challenge vaccinated rabbits by aerosol. Anthrax vaccination gave 90% to 100% protection against an aerosol challenge in the rabbit with these 6 strains that were most virulent in the guinea pig. Thus, the anthrax vaccine protects the rabbit against a lethal aerosol challenge with all strains tested to date.

A press conference on February 3, 1998 from the Los Alamos National Laboratory suggested that the FDA-licensed anthrax vaccine might be ineffective against a mixture of strains of *Bacillus anthracis*. Scientists from Los Alamos National Laboratory have described identification, using gene probes, of multiple strains of anthrax in tissue specimens obtained from victims of the 1979 Sverdlovsk anthrax incident. The laboratory press release implied that mixtures of anthrax strains might overcome the protection afforded by anthrax vaccine. After discussions with the U.S. Army Medical Research and Materiel Command officials, the author of the press release, Dr. Walt Kirchner, Los Alamos National Laboratory, agreed to correct the press release to make it more accurate. The modification stated, in part, "…there is no experimental data or evidence to suggest that such a mixture is resistant to the FDA-licensed anthrax vaccine used by the U.S. military." The protective antigen in anthrax vaccine induces protection at the fundamental level of anthrax pathology, making vaccine-resistance unlikely.

Other recent news releases have questioned its effectiveness against strains possibly developed by Russian scientists using genetic reengineering. Russian scientists have reported the creation of an antibiotic-resistant strain of anthrax--a relatively simple technical manipulation. They also described, in a 1997 publication, a study to improve their own anthrax vaccine. As part of that study, they genetically engineered a strain of anthrax to contain two foreign genes. That strain was resistant to the Russian anthrax vaccine unless the vaccine was modified to contain the same genes. This genetically engineered strain presumably causes disease by a different mechanism

than that used by naturally occurring anthrax strains. Such an organism would essentially be a new organism and not anthrax.

The current U.S.-licensed anthrax vaccine is considered to be highly effective against naturally occurring strains of anthrax, including antibiotic-resistant strains. This is because the vaccine acts at a fundamental level. The development of genetically engineered new organisms using anthrax or any other biological warfare agent is a potential threat that must be evaluated carefully. We are not aware, however, of any information to suggest that modified strains have been used in any context other than the research laboratory. Creating a new vaccine would require initiating a substantial research effort. Even a "new" strain hopefully would be susceptible to an antibiotic, and thus treatable. While vaccines offer the best means of protection and are an important component of our overall passive defense posture, physical protection (e.g., masks, protective clothing) is an additional critical element in our defense against biological weapons.

APPENDIX C
ILLNESSES AMONG PERSIAN GULF WAR VETERANS

When Persian Gulf War veterans returned and started reporting symptoms, some people asked if vaccines administered during the Gulf War might have caused the symptoms. Several independent expert panels addressed this and related questions head-on. These panels consisted of Veterans, civilian academic experts, scientists, health-care professionals, and policy specialists. Each of these panels included some of the nation's best scientists, who spent months or even years listening to veterans, reviewing the evidence, and deliberating the issues. In each case, the independent expert panels found that there was no evidence of any link between any vaccine and any illness common to Gulf War veterans. These reports include:

- Presidential Advisory Committee on Gulf War Veterans' Illnesses: Final Report, December 1996. < http://www.gwvi.ncr.gov/toc-f.html > Pages of Interest: second page, Executive Summary, plus pages 112-114 of the original document (Chapter 4 in the web version).
- Institute of Medicine, Health Consequences of Service During the Persian Gulf War: Recommendations for Research & Information Systems, 1996. <http://books.nap.edu/books/0309055369/html/1.html> Pages of Interest: 49-52, 55, 100.
- National Institutes of Health, Technology Assessment Workshop: The Persian Gulf Experience and Health, 29 April 1994. <http://text.nlm.nih.gov/> Search for "anthrax." Select Technology Conference Report #14. See the third section, under the caption "Vaccines."
- Defense Science Board Task Force on Persian Gulf War Health Effects, June 1994. <www.gulflink.osd.mil/dsbrpt/index.html> See chapter VIII, section E.2.

Three specific studies looking into the health of Gulf War veterans and their families were published in the *New England Journal of Medicine*.

- The postwar hospitalization experience of U.S. veterans of the Persian Gulf war. *New England Journal of Medicine* 1996;335:1505-13. <www.nejm.org/content/1996/0335/0020/1505.asp> This study concluded that "During the two years after the Persian Gulf War, there was no excess of unexplained hospitalization among Americans who remained on active duty after serving in that conflict."
- The risk of birth defects among children of Persian Gulf war veterans. *New England Journal of Medicine* 1997;336:1650-6. <www.nejm.org/content/1997/0336/0023/1650.asp> The authors concluded that "This analysis found no evidence of an increase in the risk of birth defects among the children of Gulf War veterans."
- Mortality among U.S. veterans of the Persian Gulf war. *New England Journal of Medicine* 1996;335:1498-1504. <www.nejm.org/content/1996/0335/0020/1498.asp> The authors concluded: "Among veterans of the Persian Gulf War, there was a significantly higher mortality [death] rate than among veterans deployed elsewhere, but most of the increase was due to accidents rather than disease, a finding consistent with patterns of postwar mortality among veterans of previous wars."

APPENDIX D
STUDIES OF SHORT-TERM SAFETY

U.S. Army Medical Research Institute for Infectious Disease (USAMRIID) Special Immunizations Program Study: Records from the USAMRIID Special Immunizations Program (SIP) maintained for personnel routinely immunized with the licensed anthrax vaccine show that 1,590 individuals have received 10,451 doses of the anthrax vaccine since 1973 [Pittman unpublished data]. Over 20 lots of the anthrax vaccine were used during this 25-year period. Many individuals have received over 20 doses of the anthrax vaccine. The USAMRIID monitoring system for this vaccine requires vaccinees to return for evaluation if they have a reaction they feel requires the attention of medical personnel. In the USAMRIID SIP, 4% of injections were associated with a local reaction significant enough to report to medical personnel. These local reactions consisted of redness, a temporary hardness, itching, or swelling at the injection site. Systemic reactions such as headache, fever, chills, an overall sense of feeling poorly, muscle and joint aches were reported for 0.4% of injections in this group. Local reactions occurred more frequently among females (7%) compared to males (3%). All reactions resolved without any substantial loss of time from work or long term medical effects.

Fort Bragg Study: USAMRIID investigators assessed vaccine safety and the antibody response of a cohort of soldiers to a booster dose of the anthrax vaccine and the pentavalent botulinum toxoid (an investigational vaccine used in Operation Dessert Storm) [Pittman, et. al. personal communication]. These troops had received both vaccines about 2 years earlier. A clinician examined the injection site and queried each vaccinee for systemic symptoms 30 minutes after vaccination and on days 1, 2, 3, 7, and 30 after vaccination. A positive finding on any one of those days was counted as an adverse event. This form of intense monitoring may overestimate the number of adverse events because many systemic complaints may not be causally related to vaccination. Of 486 volunteers who received both anthrax and botulinum toxoid vaccines, 20 (4.1%) showed significant systemic symptoms, including muscle aches, headache, overall feeling poorly, rash and joint pains. During the first 7 days, 44% of individuals had a mild version of one or more of these symptoms, most of which could not be attributed to vaccination. It is not possible to determine if these symptoms were causally related to the anthrax vaccine, the botulinum toxoid vaccine, or the combination. Muscle aches, joint aches and rashes were confounded by the ongoing activities of the troops, which included daily strenuous exercises and maneuvers in grassy woody areas. Local adverse events characterized by redness and swelling of 5 cm or more were noted in 22 (5%) of individuals. Nineteen percent of volunteers were noted by clinicians to have redness or swelling < 5 cm. Commonly, these injection site findings had not been observed by volunteers themselves until demonstrated by the examiners. All reactions resolved without any lasting effects.

Centers for Disease Control & Prevention (CDC) Study: Five reports of clinical trials, sponsored by the Centers for Disease Control in the 1960s, involving 16,500 doses were submitted to the FDA and reviewed for licensure of the vaccine in 1970. These studies showed reactions in 36% of recipients of an early lot of the vaccine. Later lots showed reactions in 3% to 14% of doses during the initial series. In these studies, reports for booster doses were similar, with reactions in 3% to 23% of doses administered. Reactions were mostly local and considered mild, with redness and/or swelling measuring 30 mm or less. Severe local reactions measuring

more than 120 mm occurred in 1% or less of the doses given in any study. Only 4 systemic reactions, characterized by chills and fever (2), fever (1) and feeling ill with general body aching for 24 hours (1), were reported.

Tripler Army Medical Center Adverse Event Survey: The U.S. Army is conducting a prospective, active survey of side effects temporally associated with administration of the anthrax vaccine at Tripler Army Medical Center (TAMC), Hawaii. This is not a placebo-controlled study, so it is difficult to tell what portion of reported events are due to vaccine and what portion are coincidental. So far, the cohort of 603 participants assigned to Tripler has received three vaccinations. This survey assesses: (1) self-reported side effects and duration (2) vaccinees who miss one or more days of work and/or seek medical care, and (3) VAERS reports to the FDA. Participants completed surveys after the first, second, and third dose of anthrax vaccine, at least one week after they received the immunization and indicated if they sought medical care, were hospitalized, or lost one shift of work or more. Medical records of these individuals were obtained, contact was made with their medical provider, and/or information was obtained directly from the patient to document the medical details related to the event.

Six hundred and three individuals began the anthrax vaccine series between 12 September and 13 October 1998 at TAMC. There was no control group of people not vaccinated. In decreasing order of frequency, soldiers reported any level of muscle aches (43%), fatigue (29%), headache (25%), and joint pains (20%). The survey permitted soldiers to report more than one symptom per person. In general, reported symptoms were less severe and of shorter duration with each successive inoculation. On average, 5.4% of soldiers stated they could not perform normal duties for a short period due to symptoms. This observation was noted most with the first vaccine (7.9%), and occurred less frequently with subsequent booster doses (5.1% and 3.0%, respectively). Muscle aches, headaches, joint pain, and fatigue again were the most common symptoms affecting activity. The principal investigator’s review of actual causes of medical care visits and lost duty time suggest that many had concomitant illnesses that could have been the cause of the symptoms reported.

APPENDIX E
VACCINE QUALITY ISSUES

Several recent articles in magazines and newspapers have incorrectly reported that certain lots or vials of anthrax vaccine were contaminated. At no time have contaminated lots or vials of anthrax vaccine been administered to our Service Members or shipped by DoD to any military facilities.

Anthrax vaccine lot number FAV030 passed sterility testing conducted by the manufacturer and the data was provided to the FDA prior to lot release. The FDA subsequently approved the lot for release. The lot also underwent successful supplemental testing by the manufacturer, to include sterility testing. An independent contractor oversaw supplemental testing by the manufacturer and no evidence of contamination of any type was found.

Prior to shipment of anthrax vials to DoD, the manufacturer conducts visual quality-control checks on all anthrax vials as part of its quality-assurance program. During one of these routine quality-control inspections, the manufacturer detected the presence of inert gasket or stopper material in a number of anthrax vials in lot FAV016. All anthrax vials in lot FAV016 that contained particulate gasket material were discarded. Lot-release data on lot FAV016 was subsequently sent to the FDA and, upon review, the FDA released the lot for use. Prior to the decision to immunize U.S. forces against anthrax and the initiation of DoD-mandated supplemental testing, a number of vials of lot FAV016 released by the FDA were shipped to DoD and used to immunize some Service Members and DoD laboratory workers. At no time were any of the vials from lot FAV016 contaminated with particulate gasket material ever shipped to DoD, as they had been previously discarded. During the FDA inspection of the manufacturer in February 1998, the FDA requested the manufacturer provide additional documentation on destruction of the original vials from lot FAV016 that contained the particulate material. As a good manufacturing practice, the manufacturer then quarantined all the remaining vials of lot FAV016 at the manufacturing facility pending collection of the documentation required by the FDA. In addition to meeting the FDA's requirement for documentation resulting from the February 1998 inspection, the remaining vials of lot FAV016 must also successfully complete supplemental testing before they will be removed from quarantine and shipped to the DoD for use. Since all vials from lot FAV016 previously shipped to DoD were approved by the FDA for release and had been visually checked for particulate material by the manufacturer before shipment, no recall of lot FAV016 was instituted by the manufacturer, nor was it requested by the FDA.

At no time has DoD shipped expired lots or vials of anthrax vaccine to any military facilities. However, anthrax vaccine from expired vials was inadvertently administered in an isolated incident to approximately 59 Marines at a military medical treatment facility in April 1999. Corrective measures have been implemented to prevent a reoccurrence. The incident involved a shipment of 300 vials of anthrax vaccine (3,000 doses) to a Naval Hospital in San Diego. The policy for receipt of vaccine at the facility at that time was to check the outside of the box and to sample a few vials in the box to verify the lot number and expiration date. While DoD immunization regulations require documentation of the name of the vaccine given, lot number, manufacturer, name of the health provider administering the immunization, and date when the

next dose is due, recording the expiration date in immunization or medical records is not required by military or federal regulation. Most vials in a multi-lot shipment had an August 27, 1999 expiration date, but 94 of the vials with an expiration date of March 16, 1999 were mixed throughout the shipment box. The expired vials of anthrax vaccine that were administered in April 1999 were thought to have the same August 27, 1999 expiration date, but in fact expired on March 16, 1999. As soon as the error was detected, all vials in question were returned to military supply channels. The Marines who received the anthrax immunizations from the expired vials of vaccine have been contacted and informed of the error.

All information concerning this expired-vaccine incident was forwarded to the Armed Forces Epidemiological Board (AFEB), an independent, nationally-recognized group of civilian scientific experts that advises the DoD on the prevention of disease and injury and the promotion of health. After reviewing the details of the incident on April 13, 1999, the AFEB concluded that the expired vaccine administered to the Marines posed little or no safety risk and any decrement in potency of the expired vaccine would be minimal and clinically irrelevant. The AFEB recommended that no repeat or additional doses of anthrax vaccine were required, but could be given after two weeks if a Marine insists on repeating the dose. Directly after the incident, procedures for the receipt and handling of vaccines were changed to ensure that upon receipt, the lot number and expiration of all vials of vaccine in the shipment are recorded. Upon issue, the health-care provider administering the immunization will check the expiration date of all vials of vaccine.

Rumors regarding the use of expired anthrax vaccine from lot FAV020 are unfounded. Anthrax vaccine lot number FAV020 was originally approved for release by the FDA in 1994, with an expiration date in 1996. The manufacturer of the FDA-licensed anthrax vaccine requested an extension of the expiration date and conducted additional potency testing on lot number FAV020 in 1996 to meet FDA's requirements for extending expiration. This potency testing was satisfactory and FDA subsequently re-released lot number FAV020 with the expiration date extended until 1999. The extension of the expiration date on anthrax vaccine lot number FAV020 involved the manufacturer and the FDA. The DoD was not involved in the extension of anthrax lot number FAV020. Any manufacturer of a pharmaceutical or biological product can request and receive an extension from the FDA on the expiration date of the product after federal requirements for product extension have been successfully met. It is not uncommon for a government or private-sector organization to use a pharmaceutical or biological product whose expiration date has been extended by the FDA.

Analyses performed by the Anthrax Vaccine Immunization Program Group indicate that there has been no correlation between anthrax vaccination and reports of serious adverse events (those involving loss of duty > 24 hours or hospitalization) based on (a) geographic clustering, (b) vaccine lot (manufacturing batch), or (c) active vs. reserve component status. No reports have been submitted of potentially contaminated vaccine vials.